Development of the HPV 16 / 18 Cervical Cancer Vaccine

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Cervical Cancer Vaccines

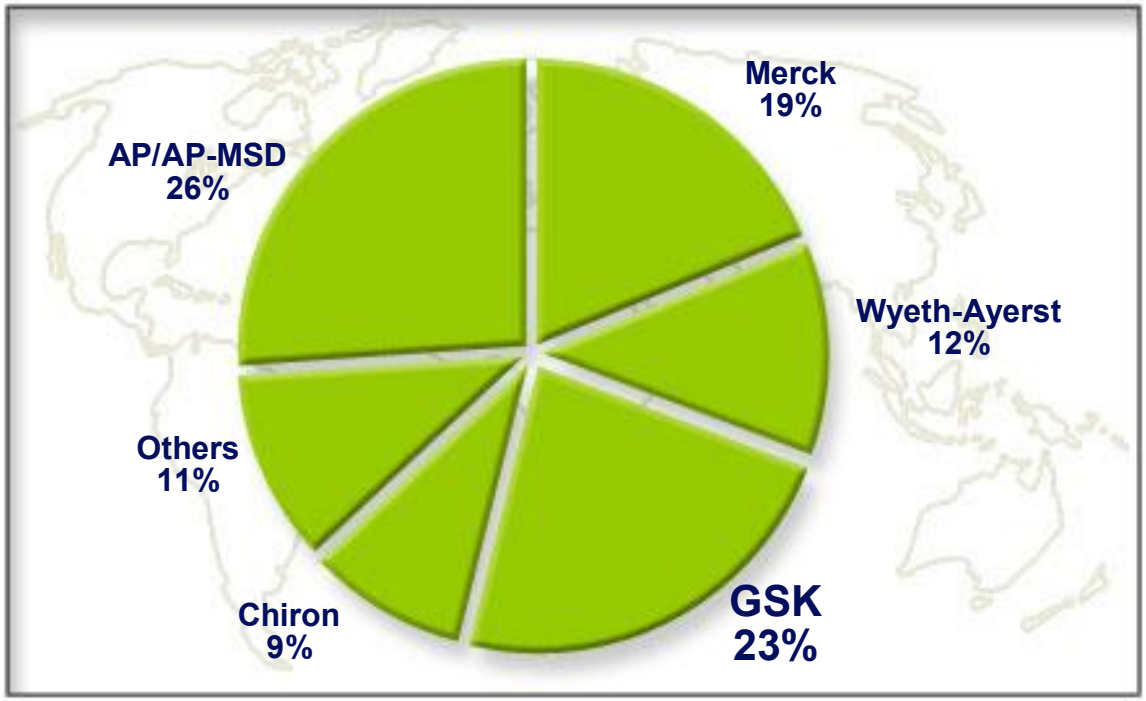
August 3, 2006

Overview

- GSK Biologicals
- Search for a cervical cancer vaccine
- GSK HPV 16/18 candidate vaccine
  - Novel adjuvant system resulting in strong and sustained immune responses
  - Focus on cervical cancer prevention
- Clinical trial data
  - Efficacy data
  - Immunogenicity data
  - Broad oncogenic protection
- Current status of the GSK HPV 16/18 candidate vaccine

GlaxoSmithKline Biologicals: One of the World's Leaders in Vaccines

Total market*: $8 billion



*2003

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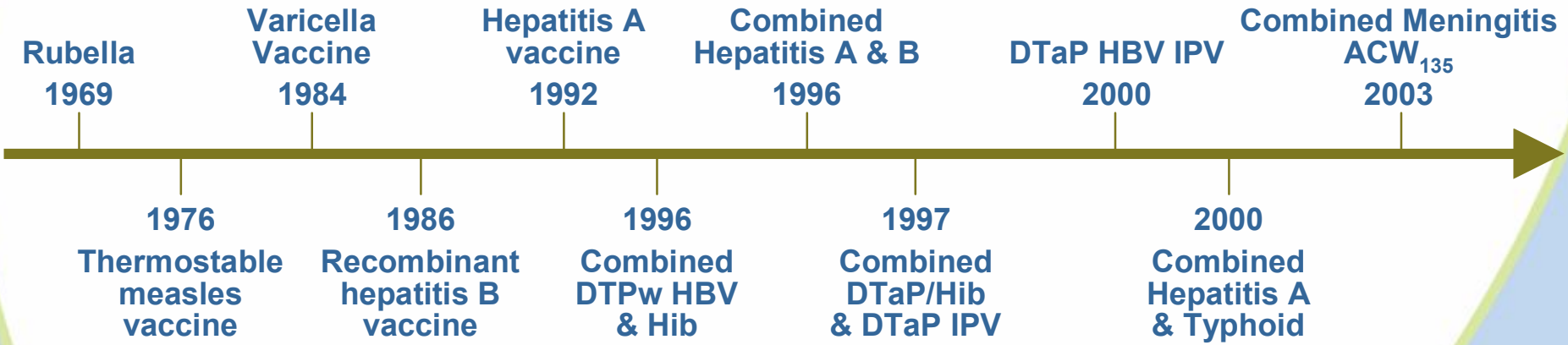
Long History of Innovation

World's Firsts



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Contributions to World's Health

- In 2004, nearly one and a half billion GSK vaccines distributed
  - Approximately 85% delivered to the developing world
  - Nearly three million doses each day
- Primary Supplier to International Health Organizations
  - UNICEF
  - WHO
  - PAHO
- GSK provides vaccines to developing world at affordable cost
  - Introduce new vaccines where most needed, not where most financially advantageous

Cervical Cancer – The Scope of the Problem

- Every two minutes a woman dies of cervical cancer worldwide
  - 10 women die every day in the U.S.
- All sexually active women are at risk of oncogenic HPV†
  - Includes women over age 25
- HPV-16 / 18 / 45 / 31 are responsible for ~80% of invasive cervical cancers worldwide°
- Adenocarcinoma of the cervix is increasing despite screening efforts[X]
  - HPV 16 / 18 / 45 / 31 responsible for 98% of cervical adenocarcinoma

† Koutsky 1997 Am J Med 1997; 102(5A): 3-8
°Munoz N et al. Int J Cancer 2004; 111: 278–85.
[X]Castellsagué J Natl Cancer Inst 2006;98:303 – 15

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Search for a Cervical Cancer Vaccine

- Safe
- Immunogenic
  - Strong immune response against oncogenic HPV
  - Provide high protective levels of antibody
- Broad protection against cervical cancer
  - Protect women from oncogenic HPV
  - Protect against the most common types
- Provide long lasting duration of protection
  - Sustained immune response
  - Long term protection

GSK's HPV 16/18 Cervical Cancer Vaccine

- Novel GSK Adjuvant System
  - AS04 (Al + MPL®)
  - To enhance immune responses
- Vaccine composition
  - 20 µg HPV 16 L1 VLP
  - 20 µg HPV 18 L1 VLP
  - 50 µg MPL®
  - 500 µg $AlOH_3$

  AS04
  - Administration schedule – 0, 1, 6 months
- Focus on cervical cancer prevention
  - Oncogenic HPV
  - Directed to women
  - Continuation of current cervical cancer screening methods

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What is an Adjuvant?

- From latin '*adjuvare*': to help
- An adjuvant can be an immunostimulant and/or a carrier
  - carrier: a compound that transports the antigen: AlOH3
  - immunostimulant: a compound that acts directly or indirectly on the immuno competent cells to increase the immune response to a given antigen : MPL®
- It is designed to increase the specific immune response intensity, quality and breadth

Novel Adjuvant: Why AS04 for HPV?

- Prevention of HPV infection requires presence of neutralizing antibodies at the site of potential infection (cervix)
- High serum antibody concentrations that then transudate to the site of the infection
- AS04 versus traditional aluminum*
  - Higher and more persistent humoral antibody response
  - Higher frequency of memory B cells

** Giannini S et al. Vaccine 2006*

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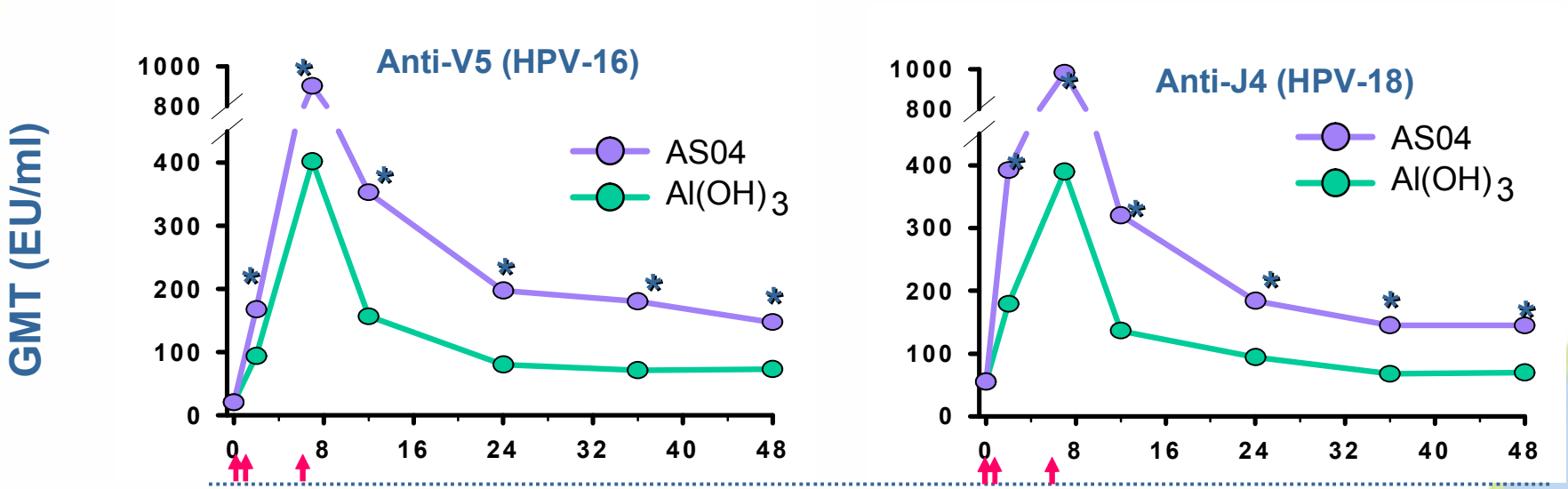
AS04 versus Aluminum

Neutralizing Antibody



Time (months)

Enhanced and Sustained Immunogenicity Over 4 Years

*** Statistically significant**

Giannini SL et al. Vaccine 2006

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Clinical Experience with AS04 Adjuvant

- AS04 used in several vaccines developed by GSK
  - Superiority of immune profile induced by AS04 *vs* alum formulations
  - 16,000 subjects received ~43,000 doses of AS04 in 40 completed and 4 ongoing studies
  - gD-AS04 (genital HSV vaccine)- Now in large-scale phase III trials including NIH collaboration)
  - FENDrix™- adjuvanted HBsAg for use in hemodialysis patients; recently approved in EU (2005)
  - Generally well tolerated

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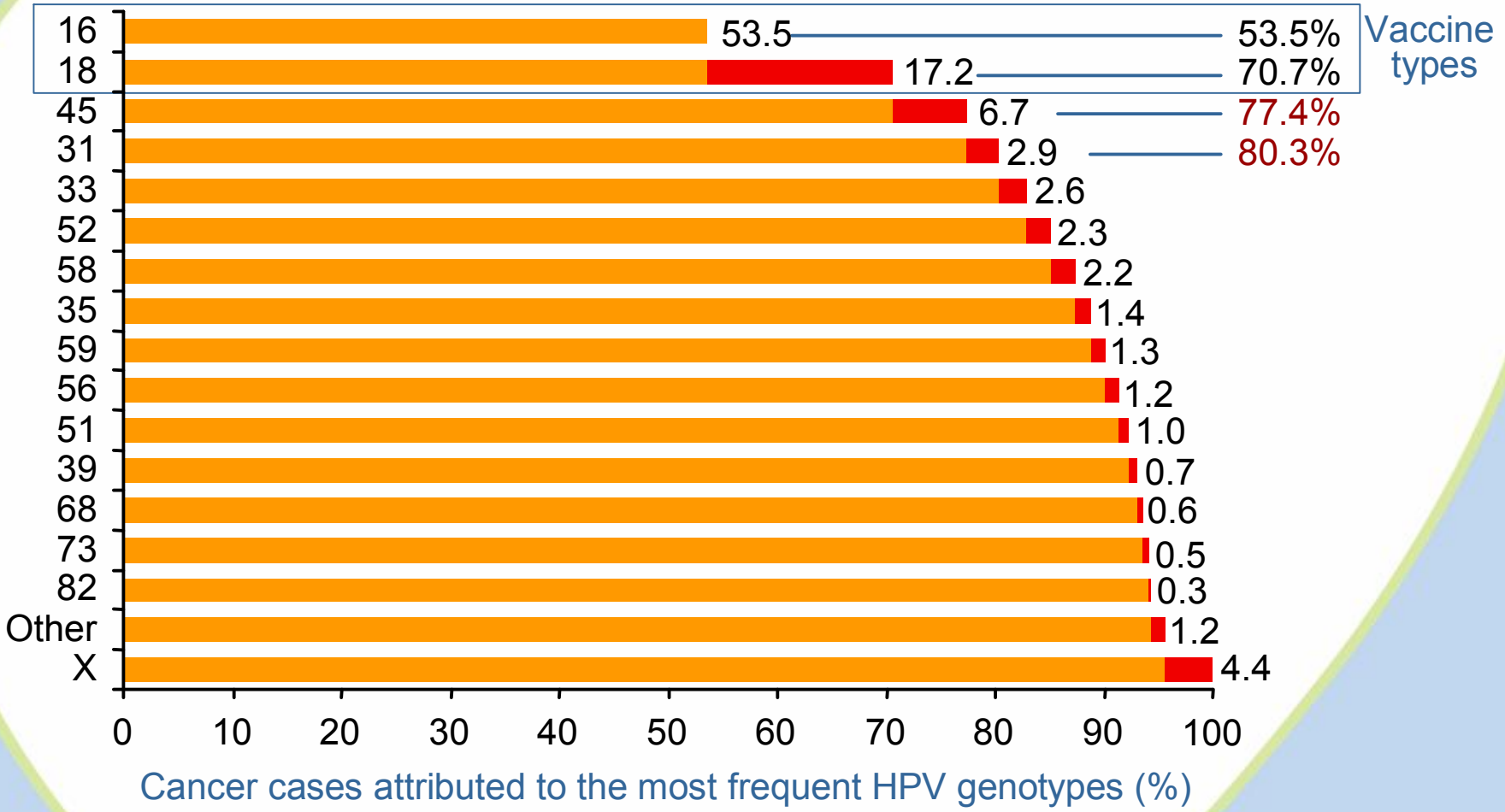
HPV Types in Cervical Cancer



Munoz N *et al*. Int J Cancer 2004; 111: 278–85.

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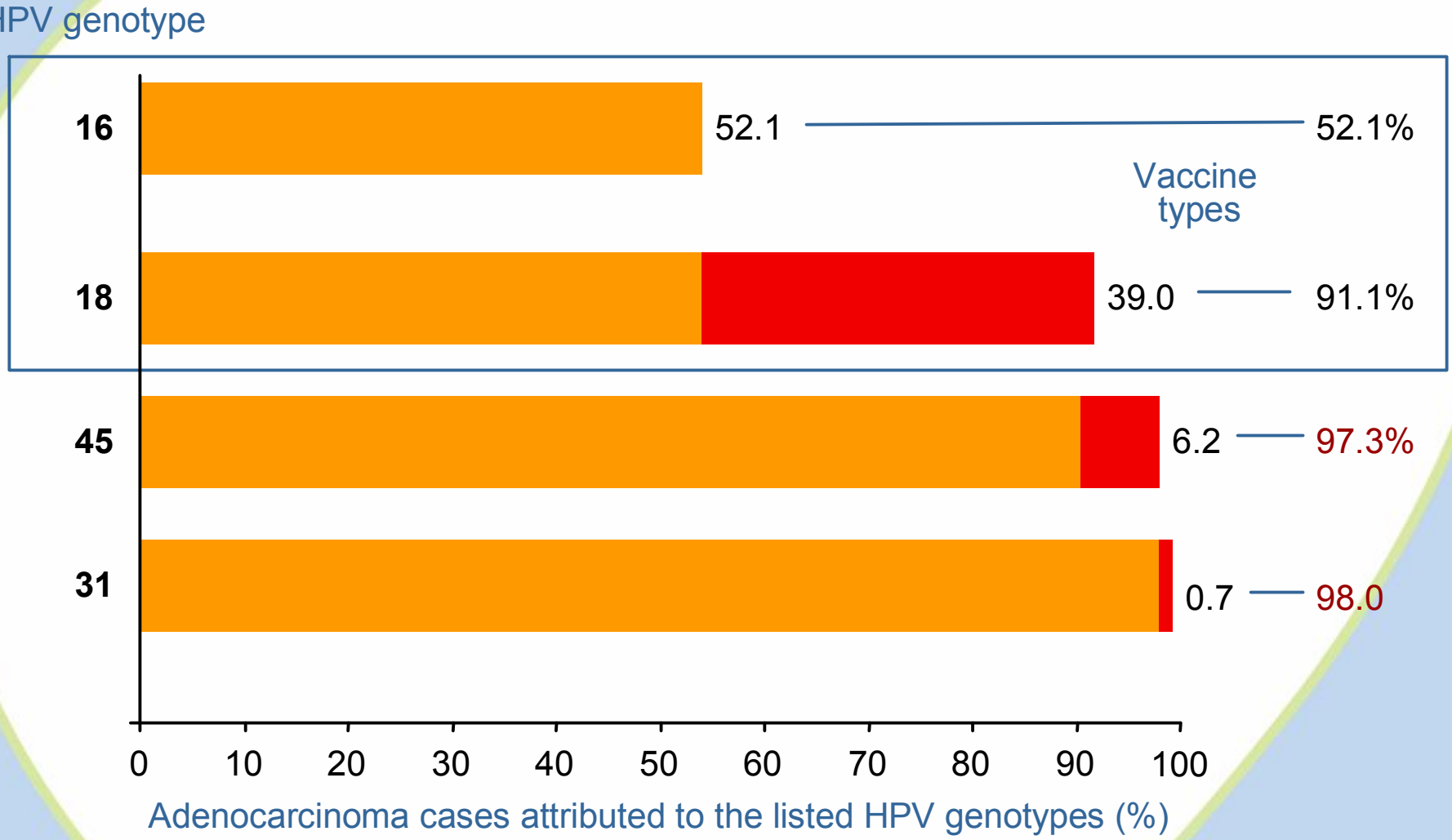
HPV Types in Cervical Adenocarcinoma



Castellsague X *et al*. JNCI 2006; 98: 303–15.

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HPV – The Disease Burden in Women

- 90.3% of cancers attributable to oncogenic HPV occur solely in women
  - Cervix – 86.5%
  - Vulva / Vagina – 3.8%

- This does not include other sites of cancer attributable to oncogenic HPV
  - Anal
  - Oro-pharyngeal
  - Mouth

Parkin DM *et al*. Int J Cancer 2006; 118: 3030–44.

Clinical Trial Data

Study HPV 001

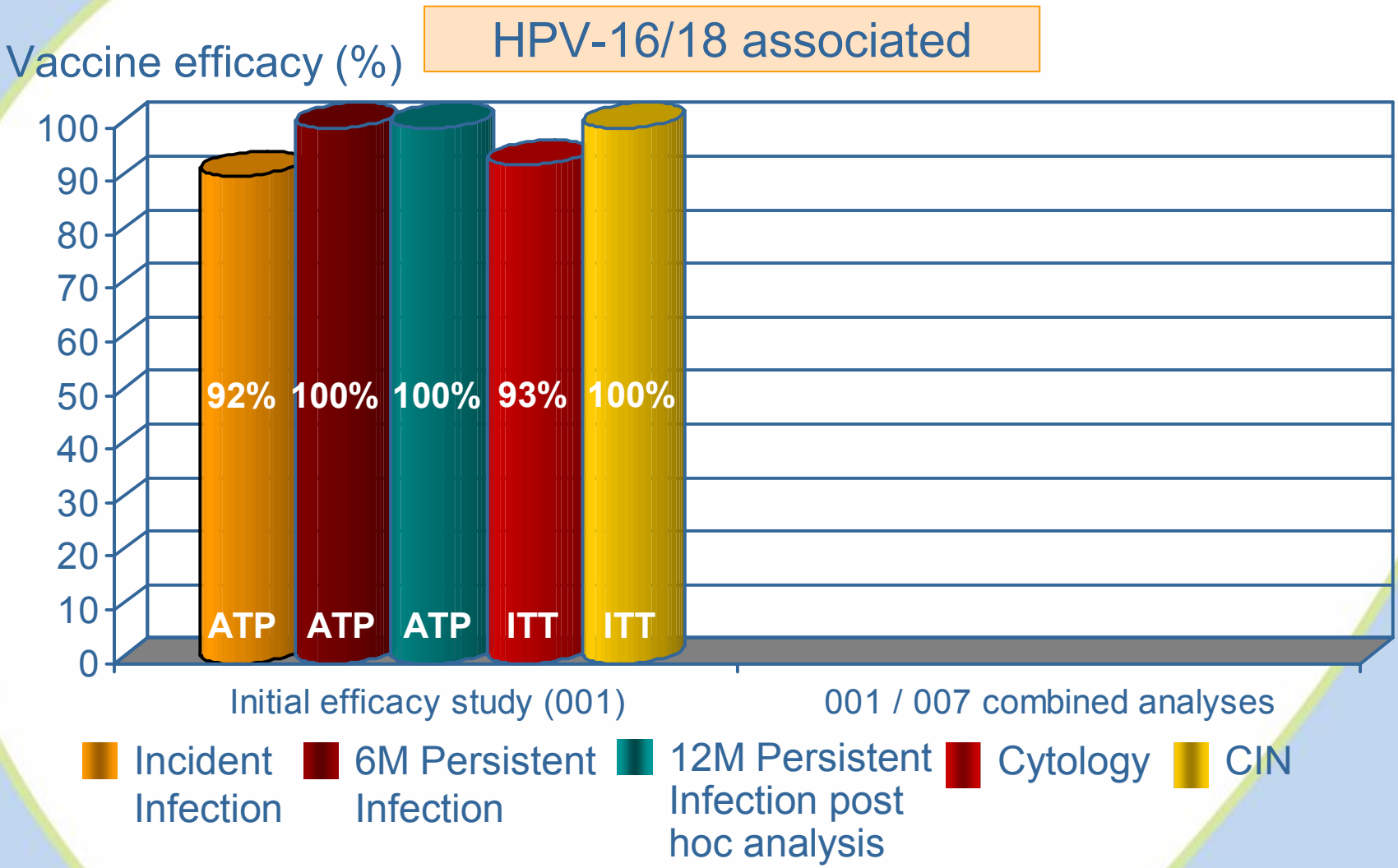

Figure based on Harper *et al*. Lancet. 2004; 364: 1757

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Study HPV 007

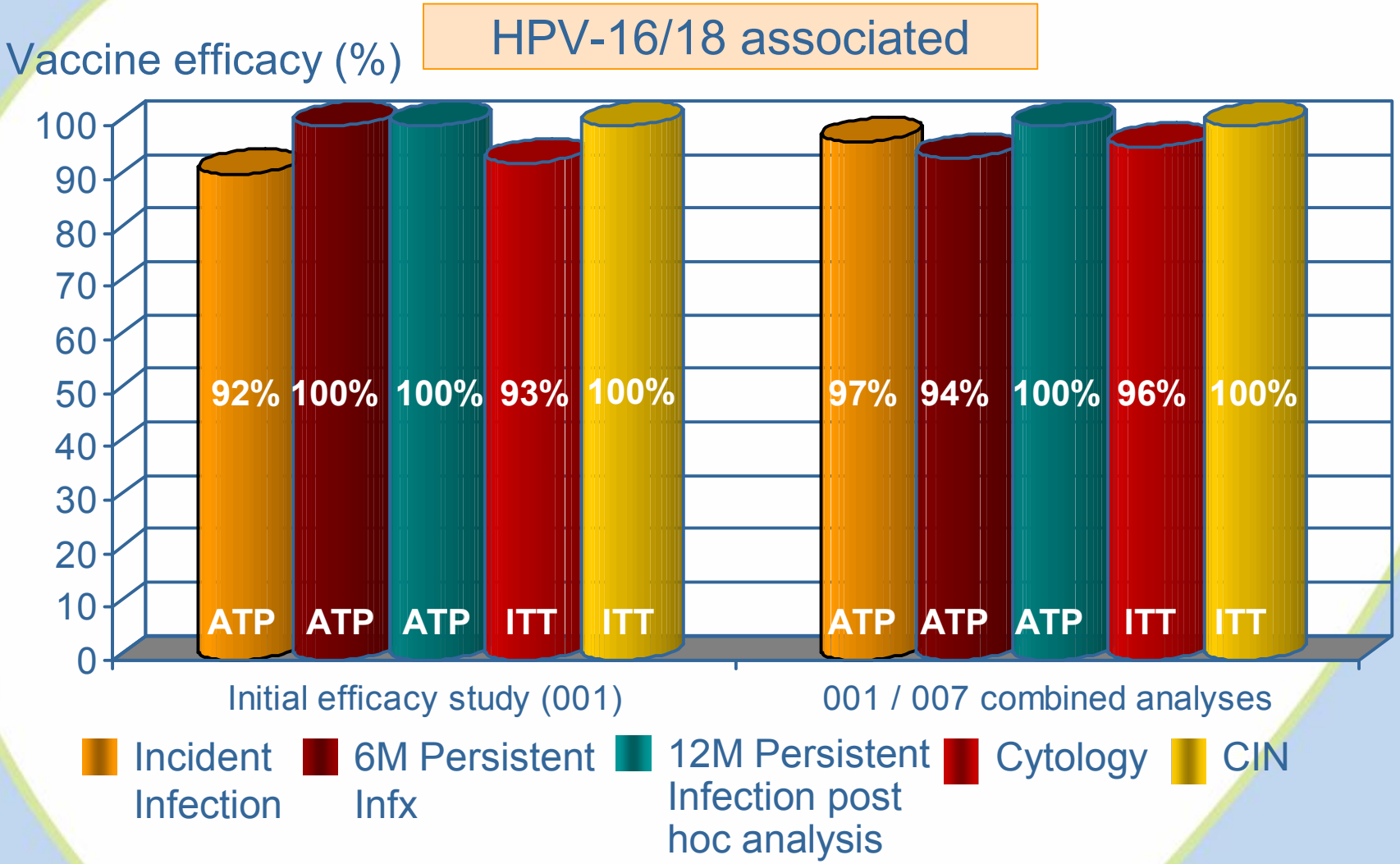

Figure based on Harper *et al*. Lancet. 2004; 364: 1757
Harper *et al*. Lancet. 2006; 367 : 124.

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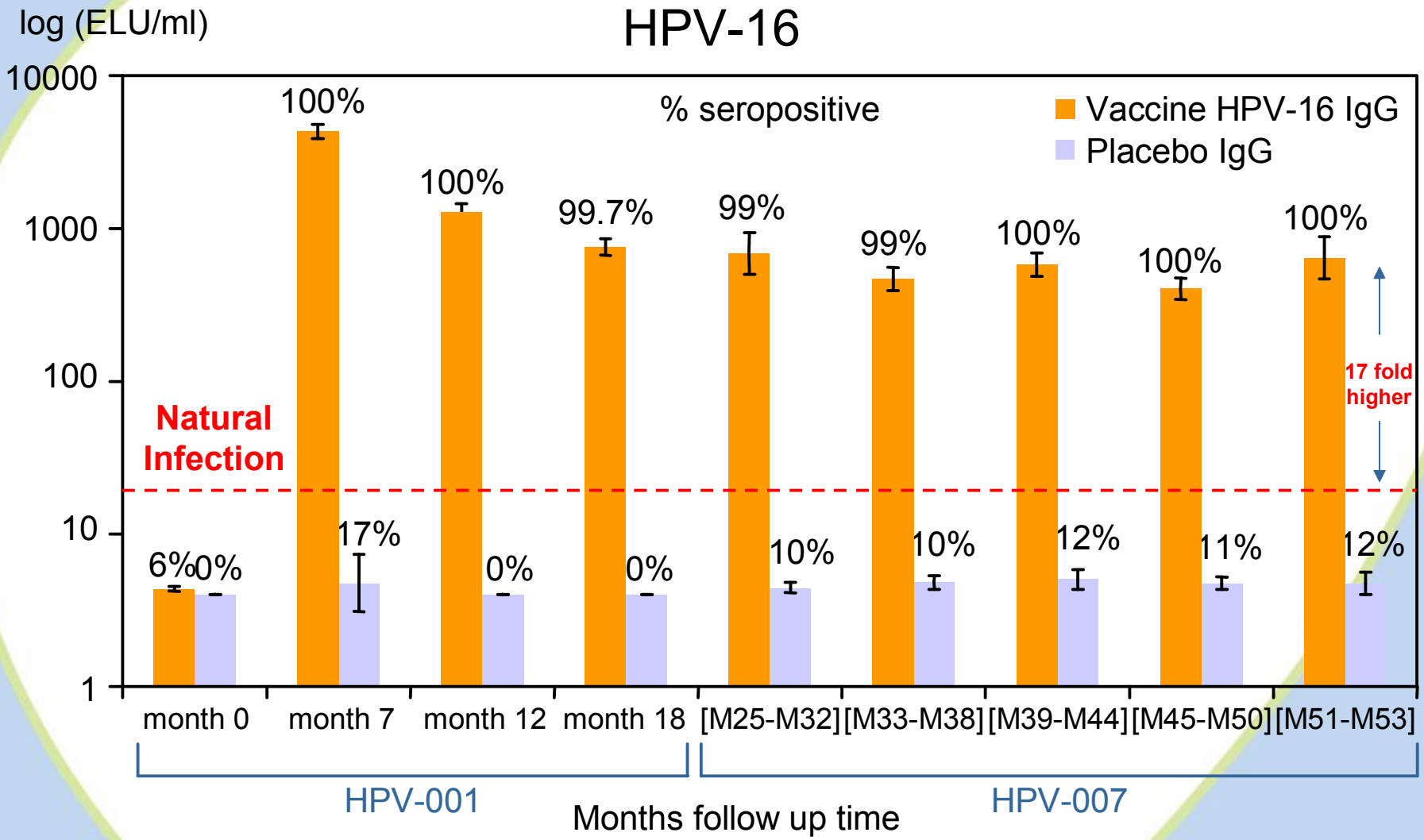
Sustained Seropositivity and High Antibody Levels up to 4.5 Years



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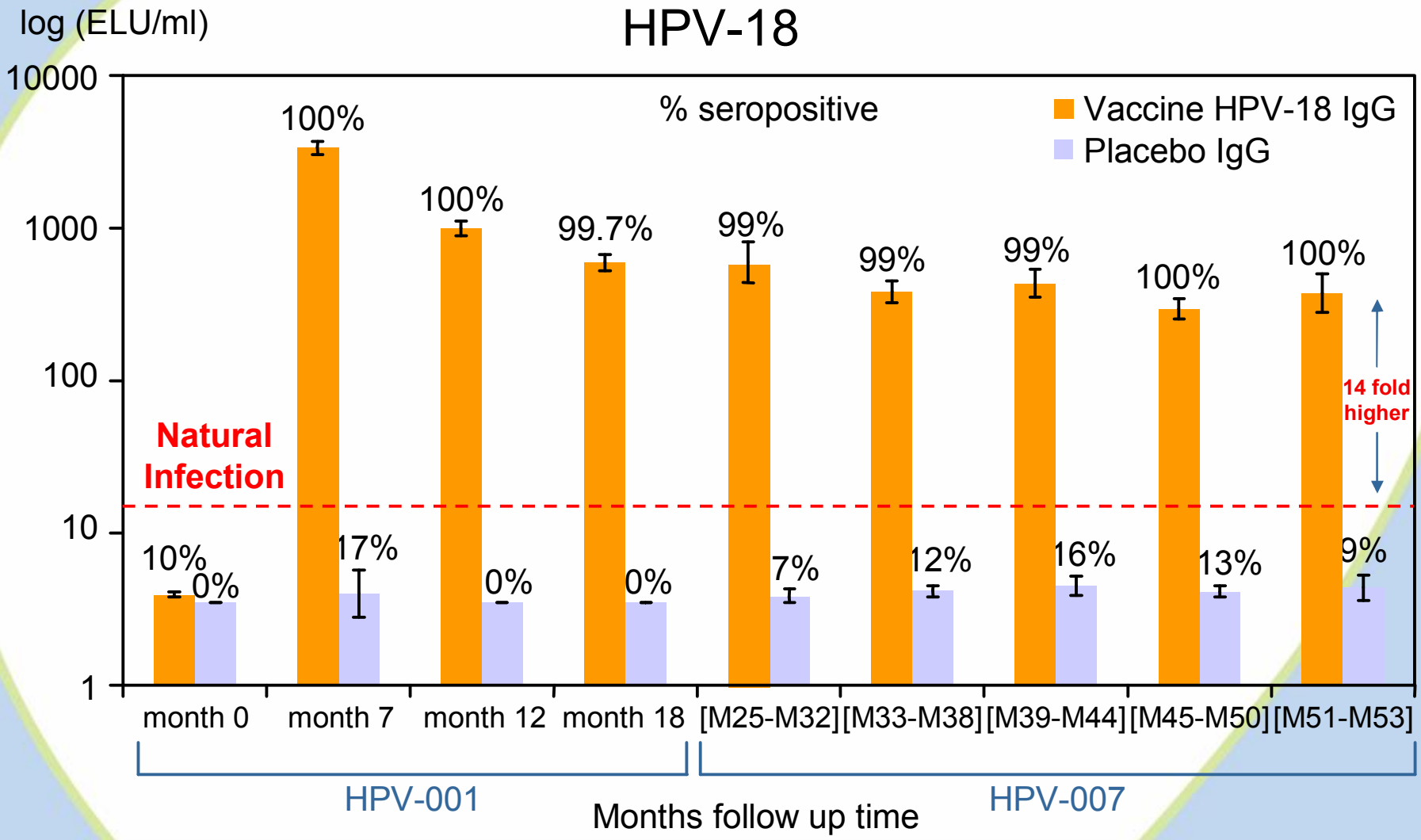

Figure based on Harper *et al*. Lancet. 2004; 364: 1757

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GSK studies 001 & 007 up to 4.5 years
First Evidence of Broader Protection

Independent of HPV DNA status

Endpoint	Vaccine		Placebo		Vaccine efficacy (%) (95% CI)	p-values	Estimated prevalence of HPV-16/18
	N	n	N	n			
≥ASCUS	505	90	497	138	39.8 (20.9-54.4)	<0.001	20-30%[1]
≥LSIL	505	41	497	70	44.6 (17.4-63.3)	0.003	25-30%[1]
CIN1+	481	12	470	24	51.5 (-0.9-77.9)	0.042	25-30%[1]
CIN2+	481	3	470	11	73.3 (-1.0-95.2)	0.033	50%[2]

Harper *et al.* Lancet. 2006; 367 : 124. ITT analysis, Conditional Exact method

[1]Clifford *et al.* Cancer Epidemiol Biomarkers Prev 2005; 14(5). [2]Muñoz et al. N Engl J Med 348;6

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GSK studies 001 & 007 up to 4.5 years
First evidence of cross protection types 45 & 31

Incident infection with most common oncogenic types beyond 16 & 18

HPV Type	Vaccine			Placebo			Vaccine Efficacy (%) (95% CI)
			Event rate (rate per 100) (95% CI)			Event rate (rate per 100) (95% CI)	
	N	n	Rate	N	n	Rate	
HPV-45	528	1	0.1 (0.0-0.4)	518	17	1.2 (0.7-1.9)	94.2 (63.3-99.9)
HPV-31	528	14	0.9 (0.5-1.6)	516	30	2.1 (1.4-3.0)	54.5 (11.5-77.7)
HPV-33	529	12	0.8 (0.4-1.4)	519	13	0.9 (0.5-1.5)	8.6 (-117.3-61.9)
HPV-52	524	40	2.8 (2.0-3.8)	515	48	3.5 (2.6-4.6)	18.6 (-26.5-47.8)
HPV-58	529	14	0.9 (0.5-1.6)	517	16	1.1 (0.6-1.8)	14.0 (-87.9-61.1)

Study not powered to evaluate cross protection against all individual types

Harper *et al.* Lancet. 2006; 367 : 124.
Combined initial efficacy and extended follow up studies

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GSK studies HPV-001 & 007
Major findings

- Duration of protection
  - Sustained efficacy against HPV 16 / 18 infections and associated lesions for up to 4.5 years
  - Longest peer-reviewed efficacy follow up for any commercial formulation
- Sustained immune response
  - Persistent antibody levels in virtually 100% of patients over 4.5 years
- Broad oncogenic protection
  - Efficacy beyond 16/18 (broader protection) largely due to cross protection against HPV types 31 and 45

Harper *et al.* Lancet. 2006; 367 : 124.

6. 2006 Lancet Online

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GSK study HPV-007
Safety Profile during Extended Follow Up

	Vaccine N (%)	Placebo N (%)
Adverse events		
Women with at least one adverse event reported	54 (15.4%)	81 (23.5%)
Adverse events reported	65	98
New Onset Chronic Disease (NOCD)*		
Women with at least one NOCD event reported	10 (2.9%)	18 (5.2%)
NOCD events reported	10	19
Serious adverse events		
Women with at least one SAE reported	16 (4.6%)	19 (5.5%)
SAEs reported	21	19

Harper *et al*. Lancet. 2006; 367 : 124.
ATP Safety analysis

*Including auto immune diseases

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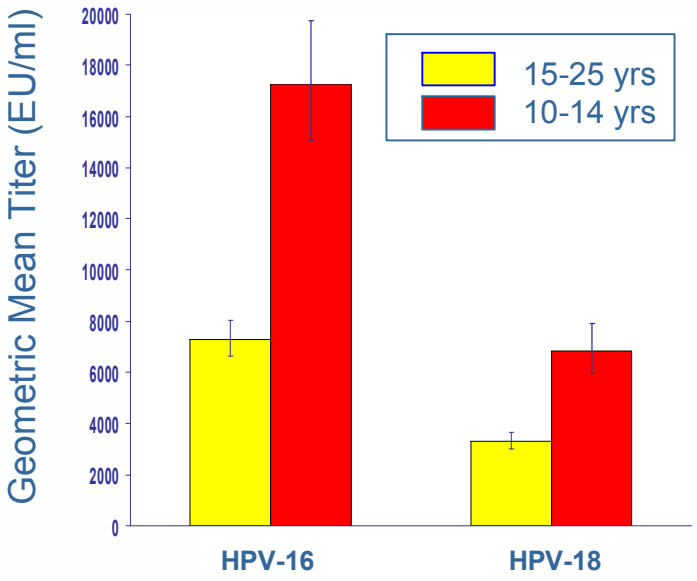
Age Bridging Trials

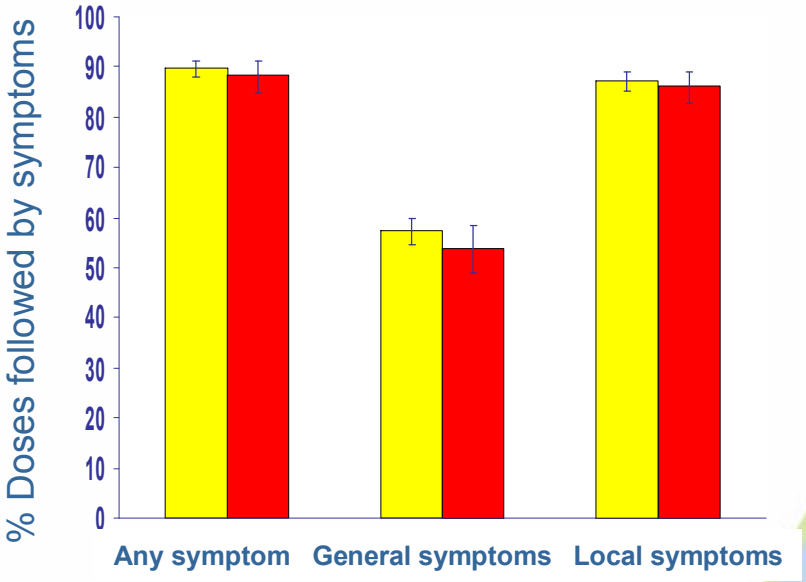
- Pre-teen/adolescent girls
  - HPV-012
    Immunological bridge 10-14 yrs and 15-25 yrs
    Safety/reactogenicity
- Women >25 years
  - HPV-014
    Immunological bridge 15-25 yrs and 26-55 yrs
    Safety

HPV-012 Results

HPV-16 and -18 ELISA GMTs (Month 7)



Solicited symptoms within 7 days (ATP cohort)



- 100% of initially seronegative subjects seroconverted to both HPV-16 and HPV-18 positive
- GMTs in 10-14 yr olds >2-fold higher than 15-25 yr olds

Dubin G, et al. Poster 4042, ICAAC, 2005, Washington, D.C. ,USA

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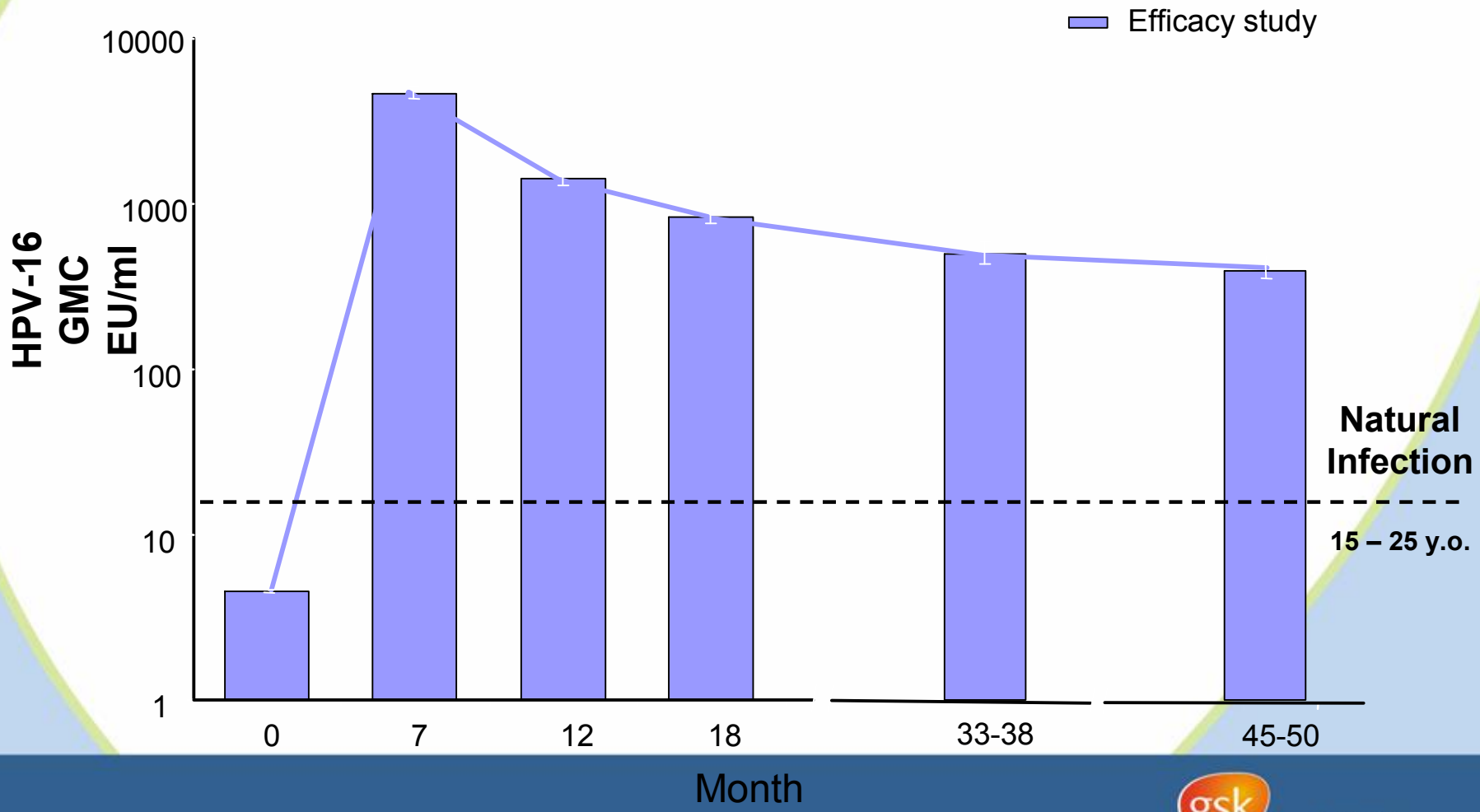
Age Bridging Trials

- Pre-teen/adolescent girls
  - HPV-012
    Immunological bridge 10-14 yrs and 15-25 yrs
    Safety/reactogenicity
- Women >25 years (HPV-014)
  - HPV-014
    Immunological bridge 15-25 yrs and 26-55 yrs
    Safety

HPV-014 - Results

- Month 7
  - 100% of subjects were seropositive to both HPV-16 and HPV-18 with high GMTs at month 7
  - Age dependent decrease in GMTs but absolute values were high

HPV-16 Antibody Levels – Efficacy Study 001 / 007



Harper et al. Lancet 2006; 367: 1247-55

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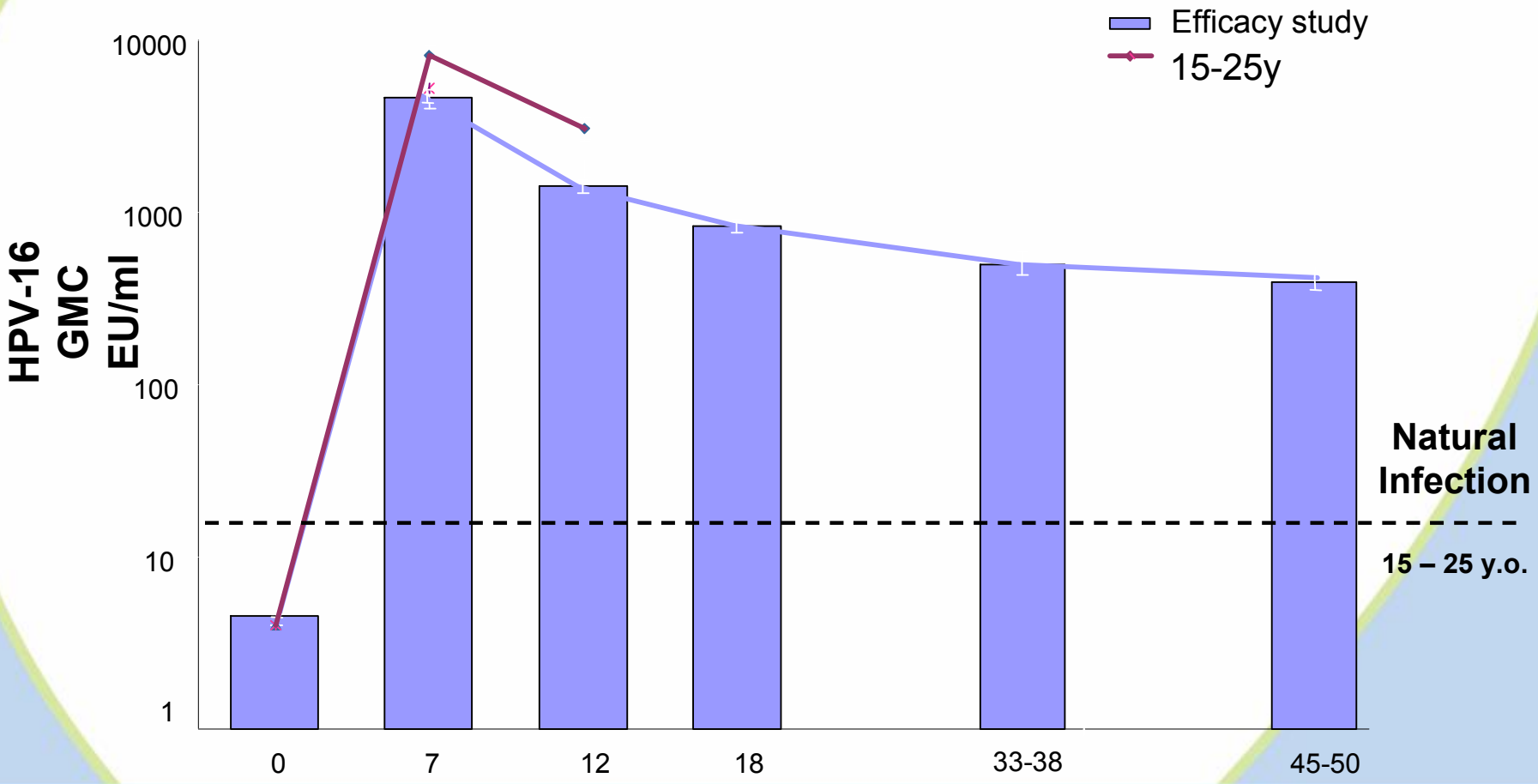
HPV 16 Antibody Levels by Age Group Study 014



Shwarz, T, et al. ASCO, 2006, Atlanta,USA
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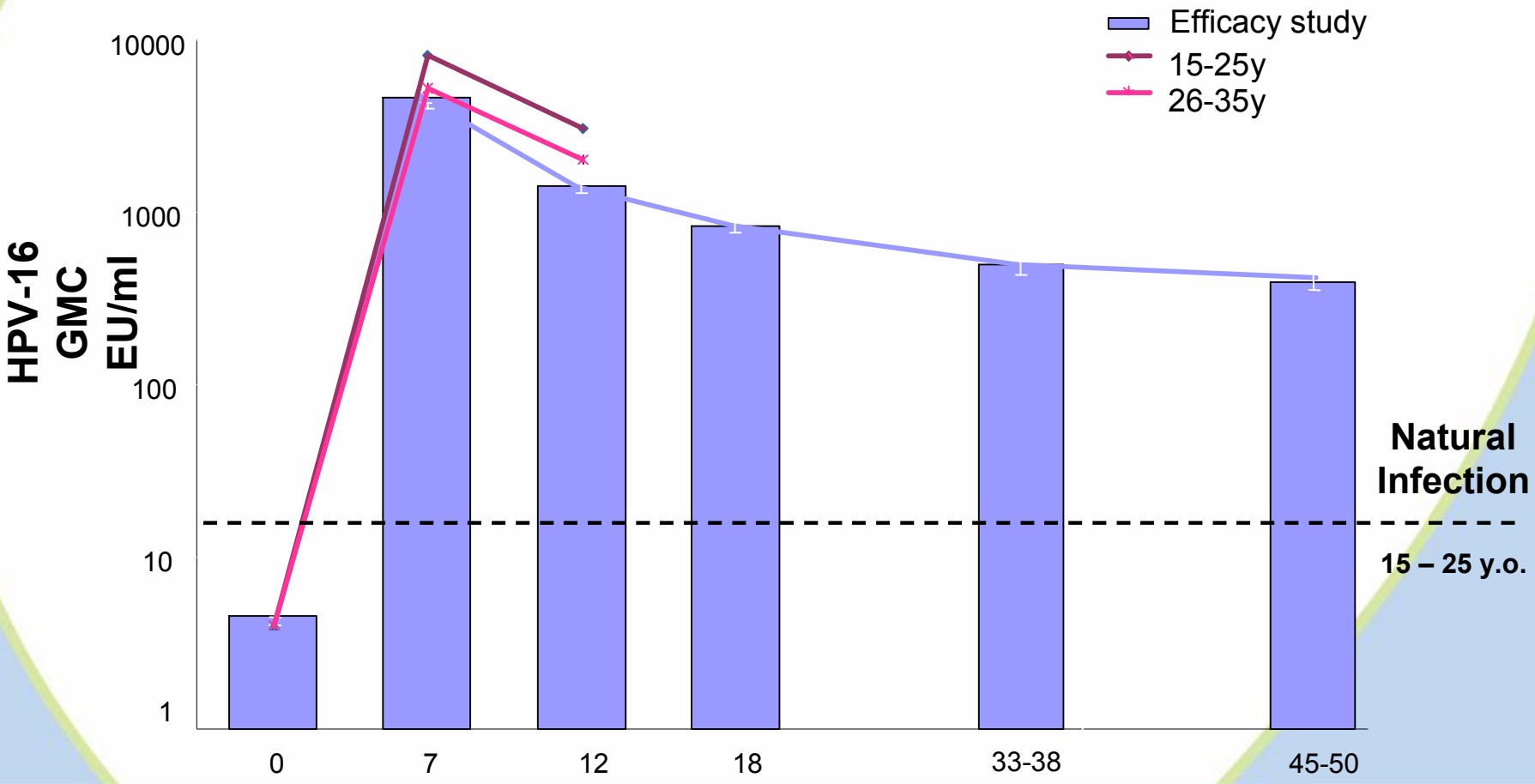
HPV 16 Antibody Levels by Age Group Study 014



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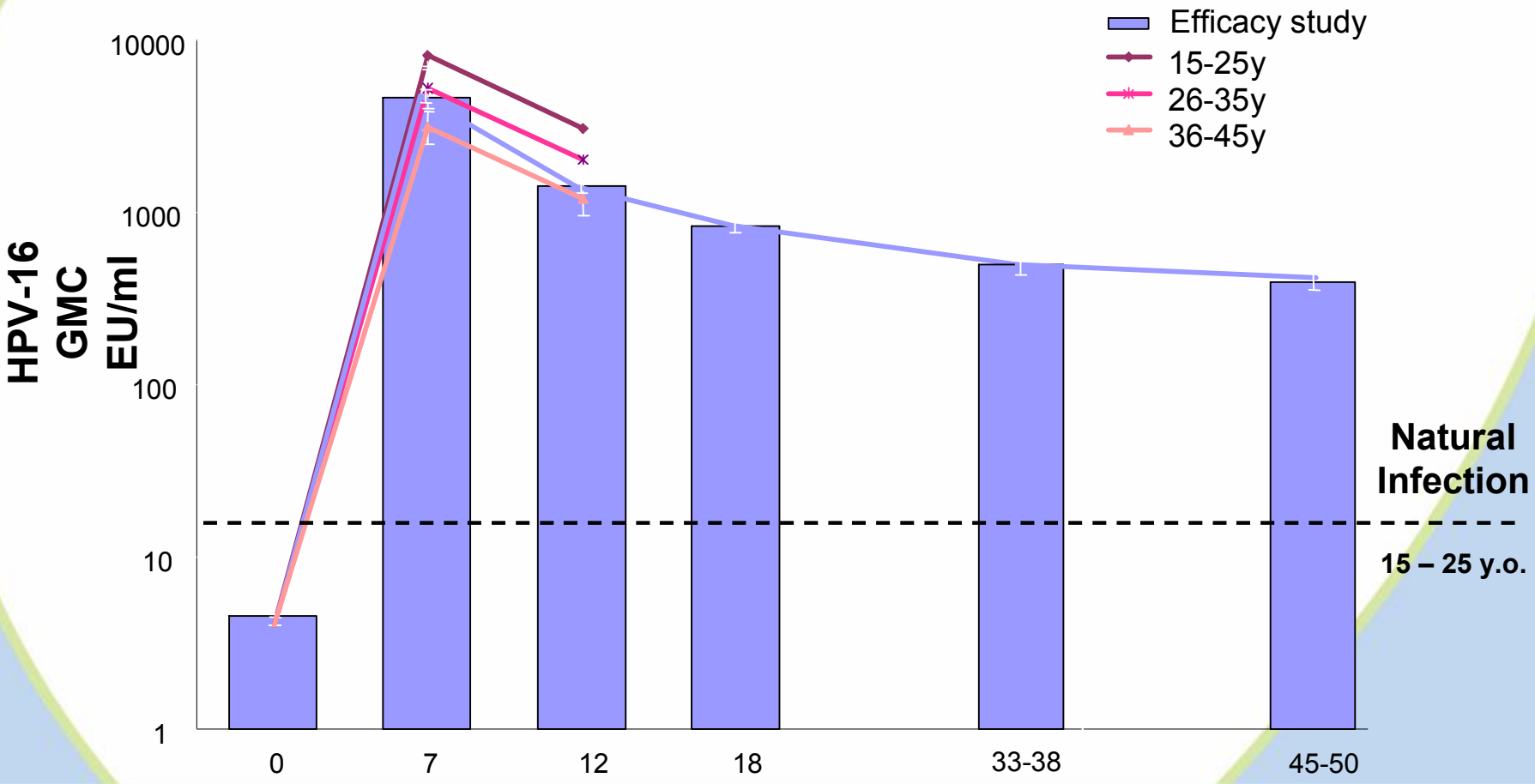

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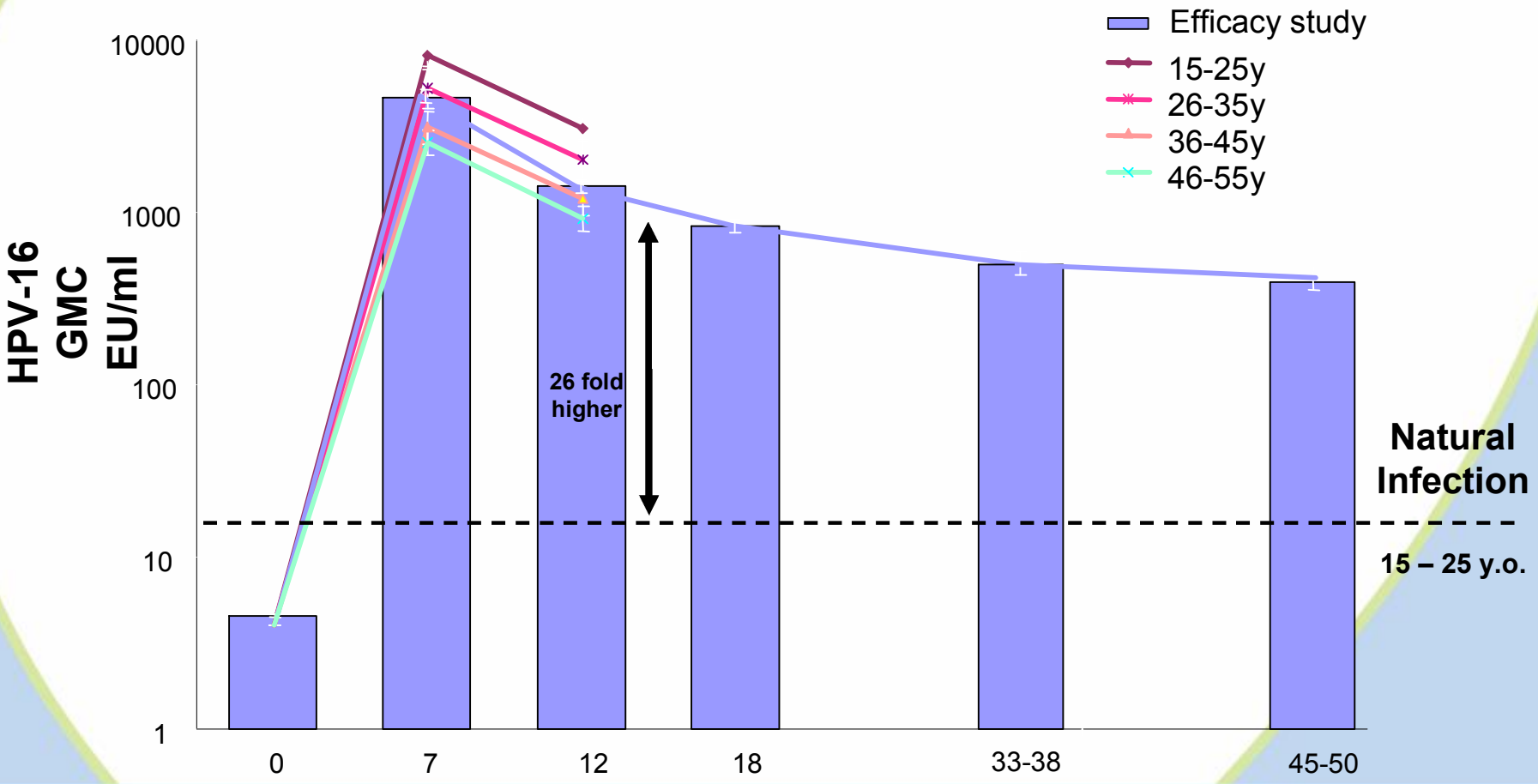
HPV 16 Antibody Levels by Age Group Study 014



Shwarz, T, et al. ASCO, 2006, Atlanta,USA
Harper et al. Lancet 2006; 367: 1247-55

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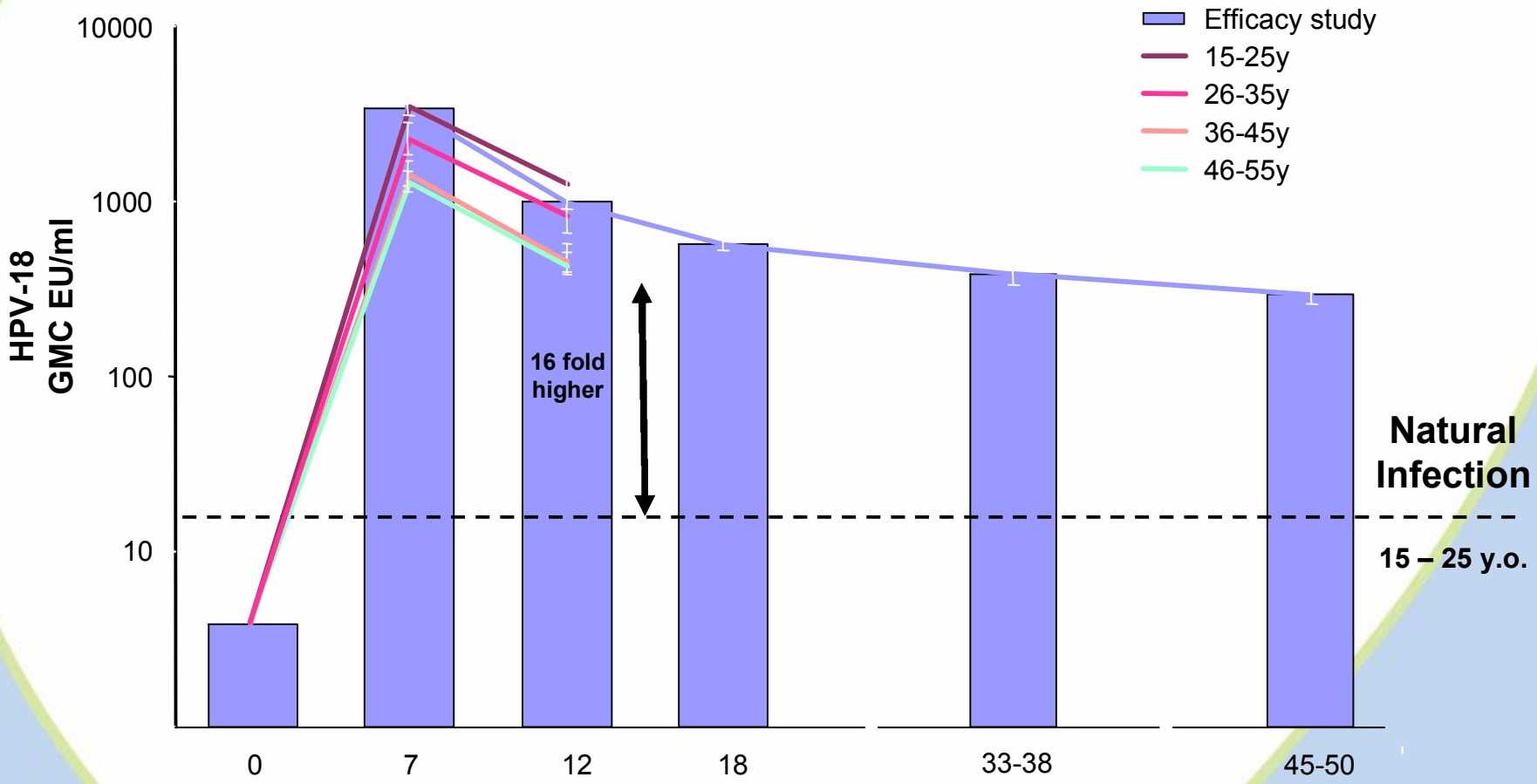
HPV 18 Antibody Levels by Age Group Study 014



Shwarz, T, et al. ASCO, 2006, Atlanta,USA
Harper et al. Lancet 2006; 367: 1247-55

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Study HPV 014 - Conclusions

In all age groups, the vaccine was:

- Generally well tolerated
- Highly immunogenic :
  - **Seroconversion** : 100% for both antigens as early as the 2nd dose of vaccine
  - **Antibody levels**
    - at least 16-26 times higher than those associated with natural HPV infection
    - ≥ levels of antibodies associated with protection against HPV infection and its associated outcomes [1]

1 Harper et al. Lancet 2006; 367: 1247-55

Shwarz, T, et al. ASCO, 2006, Atlanta,USA

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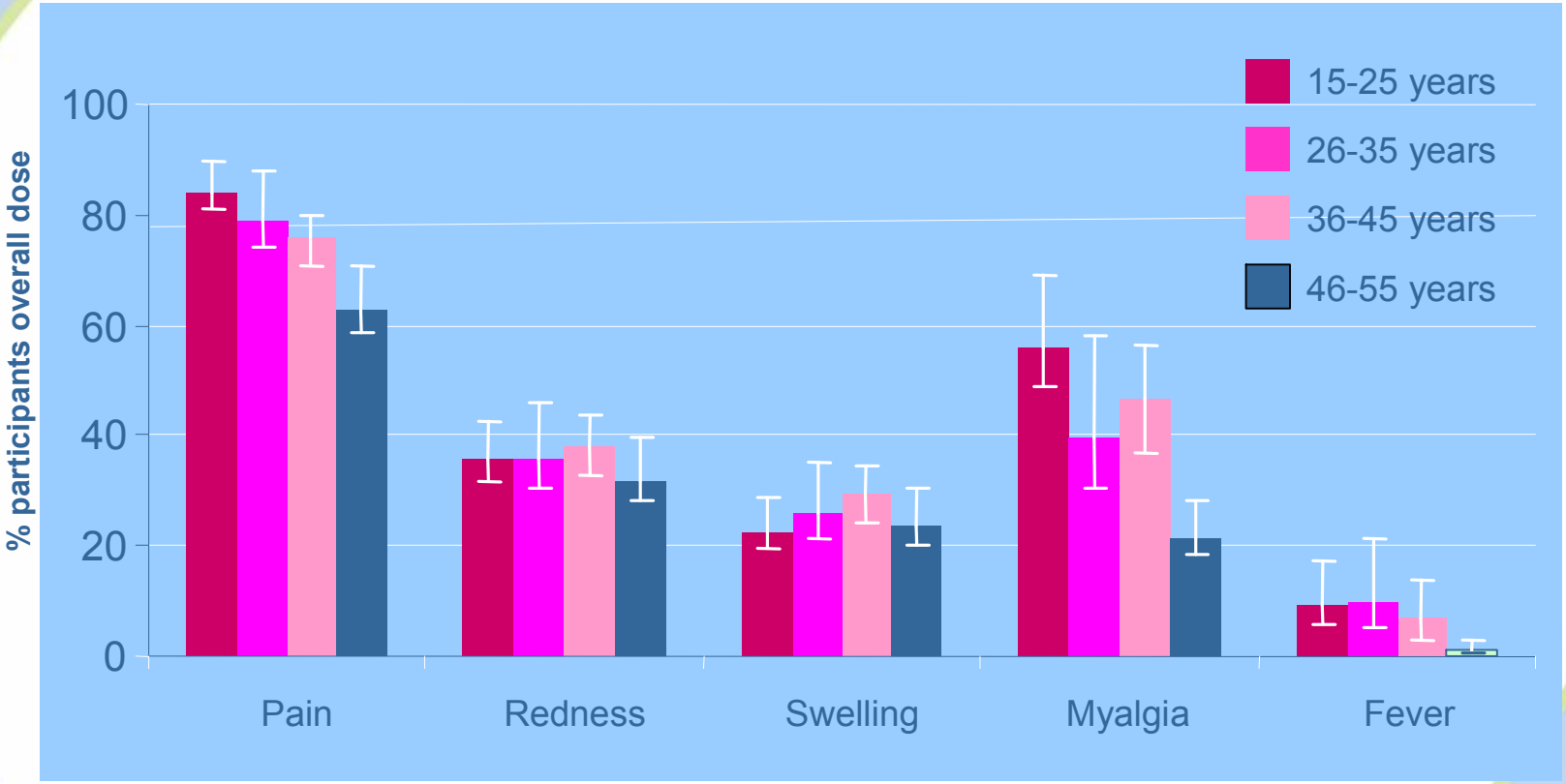
Safety profile in women 15-55 years of age



>95% study compliance

Shwarz, T, et al. ASCO, 2006, Atlanta,USA

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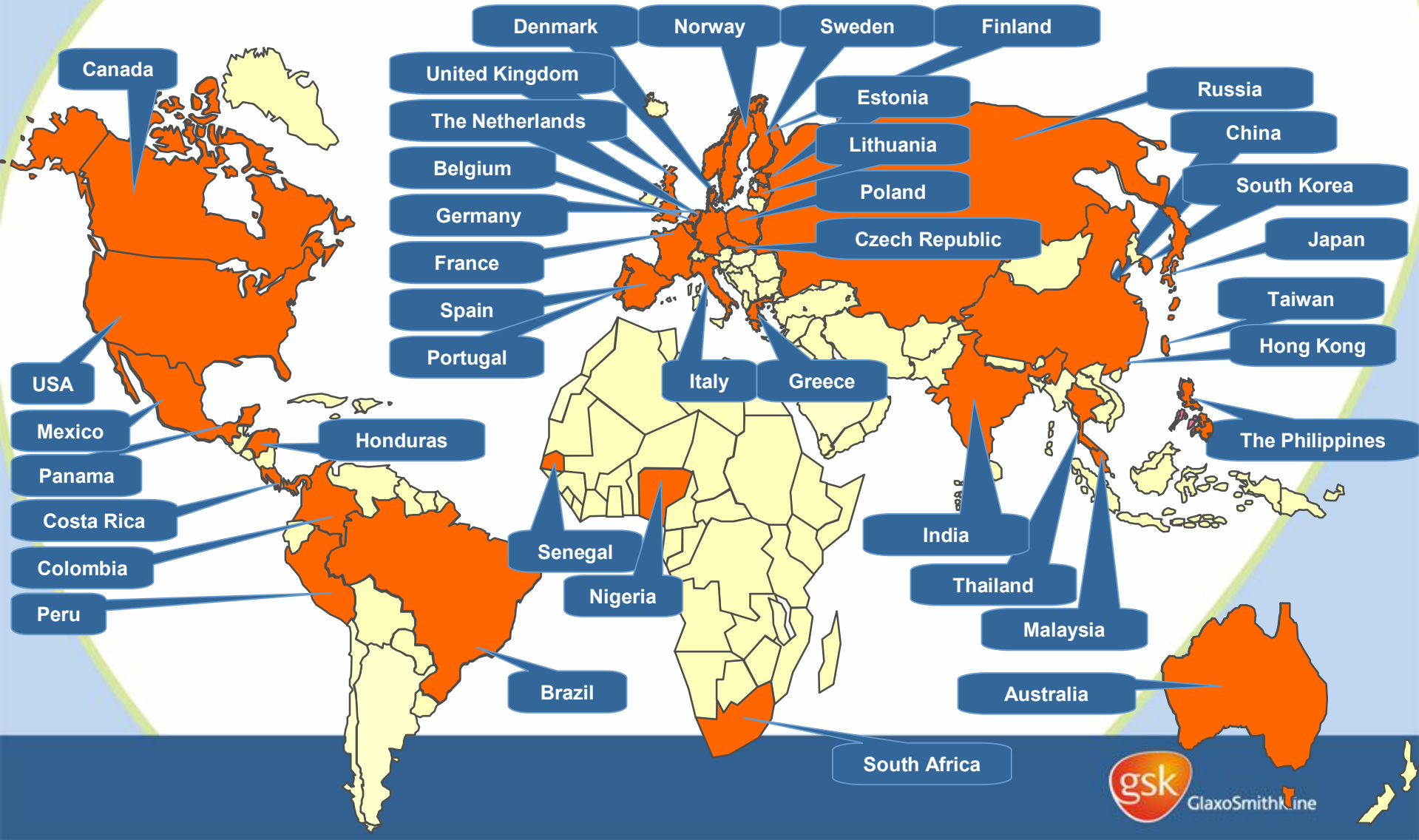
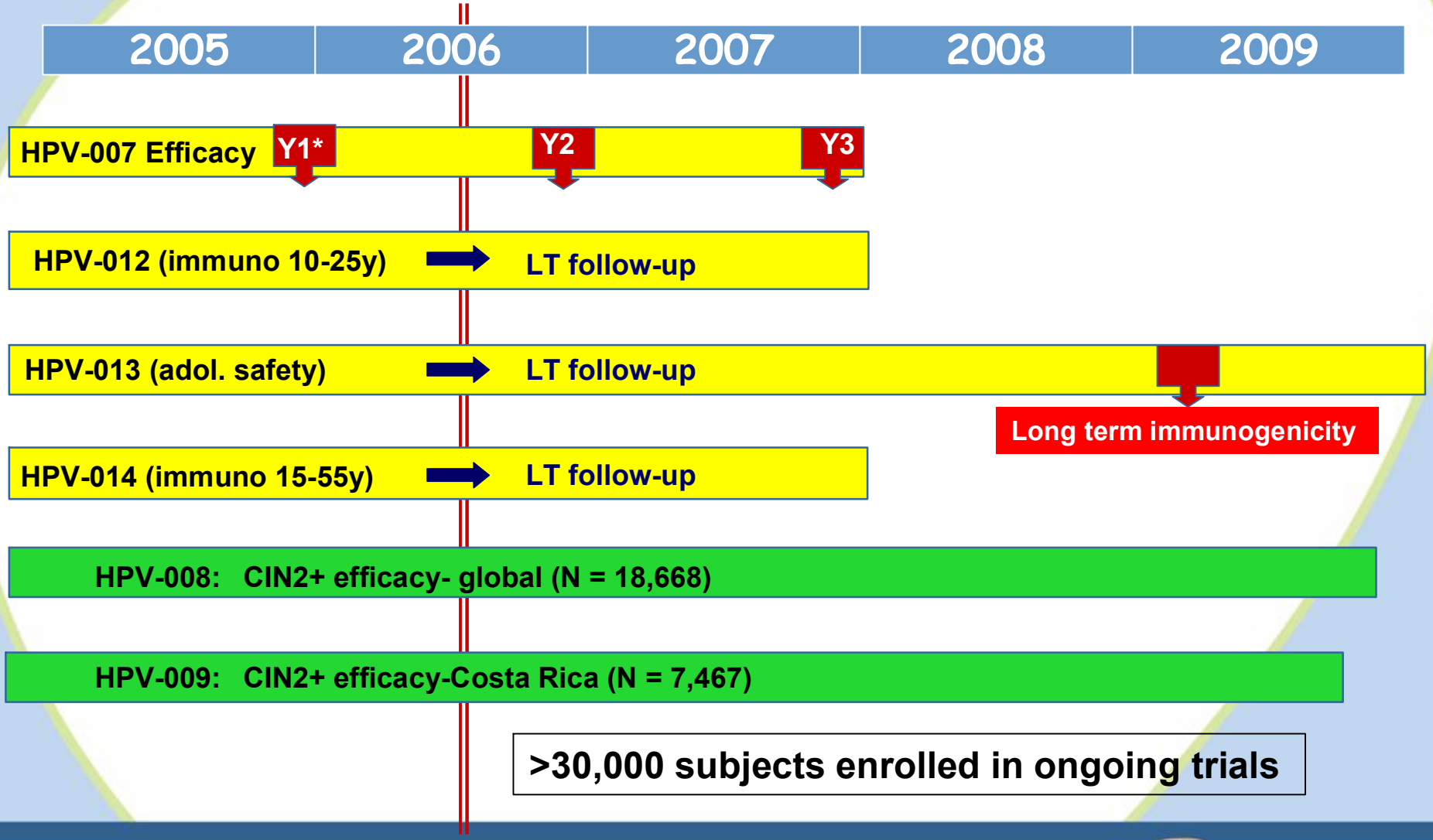
Phase III Efficacy Program

GSK efficacy study (HPV 008)	NCI supportive study (HPV 009)
Double blind, randomised, controlled	Double blind, randomised, controlled
Multi-centre (90+)	Population-based
Multi-country (14)	> 6 centres in Costa Rica
18,665 women aged 15–25 years	7465 women aged 18–25 years
CIN II+	CIN II+

GSK HPV 16/18 Vaccine
Global Clinical Development Plan



Timings: Ongoing Trials



*4 yrs of follow-up

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Conclusions

- GSK's commitment to those in need
  - Worldwide and the U.S.
- Search for a cervical cancer vaccine
  - Novel adjuvant – AS04
    - Stronger immune response compared to our vaccine formulated with Al adjuvant
  - Focused on cervical cancer
    - HPV 16 / 18
  - Directed to women

Conclusions (Cont'd)

- Safety profile
  - Well tolerated in clinical trials
- Immunogenic
  - No evidence of waning immunity to HPV 16 / 18 through 4.5 years
- Broad protection against oncogenic HPV
  - Efficacy beyond HPV 16 and 18 due to protection against HPV types 45 and 31
- Long duration of protection
  - Sustained efficacy against HPV 16 and 18 for up to 4.5 years
  - Persistent antibody levels in nearly 100% of patients